

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
NDA 50-778**

**Administrative Documents**

**ITEMS 13 & 14**  
**PATENT INFORMATION AND CERTIFICATION**

1. Active ingredient	Epirubicin (epirubicin hydrochloride)
2. Strengths	10 mg/5ml, 20 mg/10ml, 50 mg/25ml, 150 mg/75 ml, 200 mg/100 ml
3. Tradename	to be determined
4. Dosage form, Route of Administration	solution for intravenous injection
5. Applicant Firm Name	Pharmacia & Upjohn Company
6. NDA Number	21-010
7. Approval Date	to be determined
8. Patent Information	US patent applications are pending.
9. Patent Certification	Not applicable.

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Mark Griso  
Director Regulatory Affairs

Date  
11/5/98

Trade Name ELLENC Generic Name epirubicin hydrochlorideApplicant Name Pharmacia & Upjohn HFD # 150Approval Date If Known                     **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /\_\_\_/

b) Is it an effectiveness supplement?

YES /\_\_\_/ NO /X/If yes, what type? (SE1, SE2, etc.)           

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /\_\_\_/ NO /X/

If yes, NDA #\_\_\_\_\_. Drug Name \_\_\_\_\_.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

1 YES /\_\_\_/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

\_\_\_\_\_  
\_\_\_\_\_

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

\_\_\_\_\_  
\_\_\_\_\_

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

\_\_\_\_\_  
\_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # \_\_\_\_ YES /\_\_\_/ NO /\_\_\_/ Explain: \_\_\_\_\_

Investigation #2

IND # \_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

Investigation #2

YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

PS/ 6/8/99  
Patrick Guinn  
Project Manager

PS/ 6/14/99  
Robert L. Justice, M.D.  
Acting Division Director

cc: Original NDA 50-778  
HFD-150/Div. File  
HFD-150/P.Guinn  
HFD-93/Mary Ann Holovac

## PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

**NOTE:** A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 50-778

Supplement #      Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade and generic names/dosage form: ELLENCE (epirubicin hydrochloride) Action: AP ☒ AE ☐ NA

Applicant Pharmacia & Upjohn Therapeutic Class     

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate ☒ inadequate ☐

Proposed indication in this application Indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer (Stage I & II) and indicated for the therapy of patients with locally advanced or metastatic breast cancer.

**FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.**

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ☐ Yes (Continue with questions) ☒ No (Sign and return the form)

**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

☐ Neonates (Birth-1month) ☐ Infants (1month-2yrs) ☐ Children (2-12yrs) ☐ Adolescents (12-16yrs)

☐ **1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

☐ **2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

☐ **3. PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

☐ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

☐ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

☐ c. The applicant has committed to doing such studies as will be required.

☐ (1) Studies are ongoing,

☐ (2) Protocols were submitted and approved.

☐ (3) Protocols were submitted and are under review.

☐ (4) If no protocol has been submitted, attach memo describing status of discussions.

☐ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

☒ **4. PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. There is little potential for use in pediatric patients in this setting.

☐ **5. If none of the above apply, attach an explanation, as necessary.**

**ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER?** ☐ Yes ☒ No

**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from Medical Officer (e.g., medical review, medical officer, team leader)

Project Manager  
Signature of Preparer and Title

6/10/99  
Date

cc: Orig NDA/BLA # 50-778  
HFD-150/Div File  
NDA/BLA Action Package  
HFD-006/ KRoberts

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)**

(revised 10/20/97)



OFFICES OF DRUG EVALUATION  
ORIGINAL NDA/ANDA EFFICACY SUPPLEMENT  
ACTION PACKAGE CHECKLIST

NDA # 50-778 Drug: ELLENCE (epirubicin hydrochloride)  
(formerly 21-010)  
Applicant: Pharmacia & Upjohn Chem/Ther/other Types: \_\_\_\_\_  
CSO/PM: Patrick Quinn Phone: (301) 594-5767 HFD- 150  
USER FEE GOAL DATE: 9/6/15/99 DATE CHECKLIST COMPLETED: \_\_\_\_\_

Arrange package in the following order (include a completed copy of this CHECKLIST):

Check or Comment

1. ACTION LETTER with supervisory signatures  
Are there any Phase 4 commitments?

AP X AE \_\_\_\_\_ NA \_\_\_\_\_  
Yes \_\_\_\_\_ No X

2. Have all disciplines completed their reviews?  
If no, what review(s) is/are still in draft?

Yes \_\_\_\_\_ No X  
Chemistry

3. LABELING (package insert and carton and container labels).  
(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)

Draft 6/10/99  
Revised Draft \_\_\_\_\_  
Final \_\_\_\_\_

3b. 3 Most Recently Approved Labels

4. PATENT INFORMATION  
5. EXCLUSIVITY CHECKLIST  
6. PEDIATRIC PAGE (all NDAs) (Could Not Complete Electronically)  
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).

Included  
Included  
Included  
Included

8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES Completed sites were  
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. for metastatic breast cancer  
If no audits were requested, include a memo explaining why.

Canadian Sites Pending Site Visit in July 1999 for adjuvant therapy

9. REVIEWS & MEMORANDA:

- ✓ DIVISION DIRECTOR'S MEMO | If more than 1 review for any  
✓ GROUP LEADER'S MEMO | 1 discipline, separate reviews  
✓ MEDICAL REVIEW | with a sheet of colored paper.  
✓ SAFETY UPDATE REVIEW | Any conflicts between reviews  
✓ STATISTICAL REVIEW | must have resolution documented  
✓ BIOPHARMACEUTICS REVIEW  
✓ PHARMACOLOGY REVIEW (Include pertinent IND reviews)  
    ✓ Statistical Review of Carcinogenicity Study(ies)  
    ✓ CAC Report/Minutes  
✓ CHEMISTRY REVIEW  
    ✓ Labeling and Nomenclature Committee Review Memorandum  
    ✓ Date EER completed \_\_\_\_\_ (attach signed form or CIRT's printout)  
        FUR needed \_\_\_\_\_ FUR requested \_\_\_\_\_  
    ✓ Have the methods been validated?  
    ✓ Environmental Assessment Review / FONSI  
✓ MICROBIOLOGY REVIEW  
    ✓ What is the status of the monograph?

N/A  
N/A  
Included  
Included  
Included  
Included  
Included In The Review  
N/A  
Included  
Included  
OK X No \_\_\_\_\_

Yes (attach) \_\_\_\_\_ No X  
Review X FONSI \_\_\_\_\_  
Approval

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes

Included

11. MINUTES OF MEETINGS

Date of End-of-Phase 2 Meeting: Guidance 4/9/98  
Date of pre-NDA Meeting: 7/23/99  
CMC pre-NDA Meeting 7/23/99

Included

12. ADVISORY COMMITTEE MEETING MINUTES  
or, if not available, 48-Hour Info Alert or pertinent section of transcript.

Quick Minutes ✓ Info Alert \_\_\_\_\_  
Transcript \_\_\_\_\_ No mtg \_\_\_\_\_

13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS

Included

14. If approval letter, has ADVERTISING MATERIAL been reviewed?  
If no and this is an AP with draft labeling letter, has advertising material already been requested?

N/A Yes \_\_\_\_\_ No \_\_\_\_\_  
Yes, documentation attached \_\_\_\_\_  
No, included in AP ltr \_\_\_\_\_

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)

Included

16. INTEGRATED SUMMARY OF SAFETY (from NDA)  
revision: 5/14/96

Included

## FDA Question

"Doxorubicin in combination with paclitaxel has been reported to result in a high incidence of cardiotoxicity. Are there similar studies for epirubicin in combination with paclitaxel or docetaxel?"

## P&U Response

In the majority of phase I/II studies recently reported in the literature (table below) the combination of epirubicin with paclitaxel or docetaxel appears not to induce a higher incidence of major cardiac toxicity, in particular CHF.

Combination Epi+ taxol in first or second line in ABC

Author	Reference	Ph	Regimen	N.Pts	Stage	Cardiac Toxicity
Catimel	Sem Oncol 23(1,suppl.1):24-27,1996	I	Epi 50-60 mg/msq + Taxol 110-250 mg/msq q3w	31	ABC 19 pretreated with Dx*	CHF: 7% (2/31) LVEF↓: 13%
Luck	Sem Oncol 23(1,suppl.1):33-36,1996	II	Epi 60 mg/msq + Taxol 175 mg/msq q3w	57	ABC 15% pretreated with Dx; 46% with RT**	CHF: 0% LVEF↓: 0%
Carmichael	Sem Oncol 24(5,suppl.17):44-47,1997	II	Epi 75 mg/msq + Taxol 200 mg/msq q3w	35	ABC 1 <sup>st</sup> +2 <sup>nd</sup> line	CHF: 0% LVEF↓: 0%
Ventriglia	EJC 33 (suppl8):S157,1997	II	Epi 70 mg/msq + Taxol 200 mg/msq q3w	16	ABC 6 pretreated with Dx; 11 with RT	CHF: 0% LVEF↓: 0%
Conte	Sem Oncol 23(5,suppl.11):28-31,1996	I/II	Epi 90 mg/msq + Taxol 135-225 mg/msq q3w	29	ABC 14 pretreated with Dx; 16 with RT	CHF: 0% LVEF↓: 8%
Luck	Sem Oncol 24(5,suppl.17):35-39,1997 Oncology 12(1, suppl. 1): 36-39,1998	II	Epi 60 mg/msq + Taxol 175 -225 mg/msq q3w vs Epi 90 mg/msq + Taxol 175 - 225mg/msq q3w	43 25	ABC	CHF: 4 % (1/25)
Ries	Sem Oncol 24(1,suppl.17):48-51,1997	I/II	Epi 100 mg/msq + Taxol 135-180 mg/msq q2w +GCSF	16	ABC 3 pretreated with Dx	CHF: 0% LVEF↓: 0%
Kohler	Sem Oncol 24(5,suppl.17): 40-43,1997	II	Epi 25 mg/msq + Taxol 80 mg/msq vs Epi 35 mg/msq + Taxol 80 mg/msq	25 10	ABC 2 <sup>nd</sup> line	CHF: 0% LVEF↓: 0%

\* Dx = Doxorubicin

\*\* RT = Radiotherapy

## Combination Epi + taxotere in first line in ABC

Author	Reference	Ph	Regimen	N.Pts	Stage	Cardiac Toxicity
Pagani	Ann Oncol 10:539-545, 1999	I	Epi 75-120 mg/msq + Taxotere 75-85 mg/msq q3w	42	ABC 1 <sup>st</sup> line no previous anthracyclines	CHF: 0%
Panagos	Ann Oncol 9 (suppl 4), Abstr. 97P, 1998	I	Epi 60-80 mg/msq + Taxotere 70-90 mg/msq q3w	27	ABC 1 <sup>st</sup> line	Not reported
Venturini	ASCO 17; Abstr. 690, 1998	I	Epi 75-90 mg/msq + Taxotere 60-90 mg/msq q3w	25	ABC 1 <sup>st</sup> line	CHF: 0% LVEF↓: 0%
Raab	ASCO 17; Abstr. 644, 1998	I	Epi 70-90 mg/msq + Taxotere 75mg/msq q3w	12	ABC 1 <sup>st</sup> line	CHF: 0% LVEF↓: 10%
Kerbrat	ASCO 17; Abstr. 579, 1998		Epi 60-110 mg/msq + Taxotere 75mg/msq q3w	65	ABC 1 <sup>st</sup> line	CHF: 0% LVEF↓: 5%
TenBokkel Huinink	EJC 33(suppl.7): 23-25, 1997	I	Epi 120 mg/msq + CTX alternated with Taxotere 100 mg/msq q2-3w + GCSF	17	ABC no previous anthracyclines.	CHF: 0% LVEF↓: 0%
Viens	Proc Ann Meet Am Soc Clin Oncol 16, Abstr. 690, 1997	I	Epi 60-100 mg/msq + Taxotere 75mg/msq q3w	29	ABC	CHF: 0% LVEF↓: 0%
Kouroussis	Ann Oncol 10: 547-552, 1999	I	Escalating Epi + escalating Taxotere MTD= Epi 60 mg/msq+ Taxotere 80-90mg/msq	47	ABC no previous treatment	CHF: 0% LVEF↓: 9% 1 death for MI

APPEARS THIS WAY  
ON ORIGINAL

# NDA ACTION LETTER ROUTING RECORD

NDA#: 50-778

Date Received: September 13, 1999

Drug: Ellence (epirubicin HCl Inj) Division: HFD- 150

Type of Letter: AP AE NA

Drug Classification: 1P

Patent Info Received: ✓

Safety Update: ✓

Phase IV Commitment: none

## REVIEWER

## RECEIPT

## ACTION

1. Linda Carter  
Special Assistant  
to the Director

Date 9/13/99 Initials L.C.

Date 9/14/99 Initials L.C.

Comments: User fee goal date - September 15, 1999.

2. Chemistry Review

Date 9.14.99 Initials JSG

Date 9.15.99 Initials JSG

Comments: EEK ok MV pending All other CMC issues resolved.  
Labeling issues resolved after meeting with reviewer

3. Pharmacology &  
Toxicology Review

Date 9/16/99 Initials ADT

Date \_\_\_\_\_ Initials \_\_\_\_\_

Comments:

4. R. Temple, M.D.  
Director, Office of  
Drug Evaluation I

Date 9/15/99 Initials RT

Date 9/15/99 Initials RT

Returned to Division for  
Corrections \_\_\_\_\_ Forwarded \_\_\_\_\_

Letter Signed ✓

Comments:

## INTERNAL MEETING MINUTES

**MEETING DATE:** August 24, 1999      **TIME:** 2:30 p.m.      **LOCATION:** WOC2/r 5006

**NDA:** 50-778 (formerly 21-010)

**DRUG:** Ellence (epirubicin hydrochloride)

**SPONSOR/APPLICANT:** Pharmacia & Upjohn Company (P&U)

### **TYPE of MEETING:**

1. **Other:** Internal
2. **Indication:** as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer

### **FDA PARTICIPANTS:**

GCF-1 (OCC)	Kim Dettelbach	-	General Attorney, Office of Chief Counsel
	David Fox	-	General Attorney, Office of Chief Counsel
HF-35 (OPD)	Melvin Lessing, P.D., M.S.	-	Pharmacy Reviewer, Office of Orphan Products Development
	John McCormick, M.D.	-	Deputy Director, Office of Orphan Products Development
	Tan Nguyen, M.D.	-	Medical Reviewer, Office of Orphan Products Development
	Henry Startzman, M.D.	-	Medical Reviewer, Office of Orphan Products Development
HFD-101 (ODEI)	Robert Temple, M.D.	-	Director, Office of Drug Evaluation I
HFD-150 (DODP)	Julie Beitz, M.D.	-	Acting Deputy Director, Division of Oncology Drug Products
	Patrick Guinn	-	Project Manager, Division of Oncology Drug Products
	Susan Honig, M.D.	-	Medical Reviewer, Division of Oncology Drug Products
	Dianne Spillman	-	Project Manager, Division of Oncology Drug Products
	Grant Williams, M.D.	-	Medical Team Leader, Division of Oncology Drug Products

### **MEETING OBJECTIVE:**

To discuss pending NDA 50-778 Ellence (epirubicin hydrochloride) Injection. The Division would like to provide all available and relevant information to the Office of Orphan Products Development that may impact consideration of P&U's orphan drug application for epirubicin.

### **BACKGROUND:**

1. December 11, 1998      P&U orphan product application submitted.
2. July 26, 1999      OPD letter denying request for orphan designation.

As a historical note, P&U submitted a new drug application for epirubicin on July 17, 1984 and they received a non-approval on July 10, 1985. Subsequently, the applicant notified the agency that they did not plan to pursue the development of the product.

On December 15, 1998, P&U submitted a new drug application for epirubicin. At this time, P&U

elected not to respond to the NA letter of 1985 for NDA 50-595 as the new NDA contained different clinical trials and a different indication. The applicant was notified that the NDA had been assigned number 21-010. For several months the review of the new drug application proceeded without note. During the review process, a routine administrative screening of the NDA conducted in the DODP revealed that the NDA had not been assigned the appropriate antibiotic NDA number and the reassignment was made to NDA number 50-778 in May 1999. Unfortunately, P&U did not note our error. In addition, epirubicin is considered an "old" antibiotic because it had been subject to an application prior to November 20, 1997 (when FDAMA repealed Section 507 of the F D & C Act) and is not eligible for exclusivity under Waxman Hatch.

P&U vigorously appealed the classification of epirubicin as an old antibiotic but has been unsuccessful. In a meeting on August 16, 1999, Dr. Lumpkin (Deputy Center Director for Review Management, CDER) informed P&U that epirubicin's classification as an old antibiotic would stand.

At this time, P&U's only opportunity for exclusivity for epirubicin is associated with orphan designation. DODP is concerned that this product will never be available in the US because P&U does not plan to pursue marketing approval if there is no opportunity for exclusivity.

#### **DISCUSSION / DECISIONS REACHED:**

- At this meeting, attendees received a draft letter from P&U and a draft memo from \_\_\_\_\_. (both sent via fax by \_\_\_\_\_ on August 23, 1999), which respond to OPD's July 26, 1999 letter.
- DODP/ODE1 view adjuvant therapy for breast cancer as a distinct indication from metastatic breast cancer therapy. This view is reflected in the oncology community. Some of the differences in these two therapies include trial design and the fact that adjuvant therapy has curative intentions vs. palliative.
- OPD is not inclined to carve out orphan populations from larger disease settings in order to confer orphan designation.
- DODP/ODE1 stated that in the case of epirubicin, the drug can be used only once in a patient and the duration of treatment lasts less than a year. Additionally, use of the drug itself is limited because of its cardiac toxicity. As such, the population receiving epirubicin fits the definition of "medically plausible."
- There was extensive discussion regarding the numbers of breast cancer patients with various disease stages who would be eligible for adjuvant therapy.

- ODEI/DODP maintains that the toxicity of epirubicin precludes subsequent uses in the same patient; therefore, with the breast cancer incidence of <180,000/year, the number of patients eligible for this drug is considerably less than 180,000.
- OPD will send a consult to DODP asking for written clarification on these issues so that OPD can consider ODEI/DODP's arguments.
- OPD asked DODP to provide them with a memo explaining that the toxicity of this drug would preclude additional use within the same patient. DODP will also include the argument that patients with early stage breast cancer who can receive adjuvant chemotherapy should be considered a medically plausible population.
- DODP will provide a draft of their arguments to OPD for comment, prior to finalizing it.
- The DODP draft memo will also be routed to OCC (David Fox).
- NOTE: Given the PDUFA due date of September 15, 1999, DODP would prefer rapid resolution of this issue.

#### UNRESOLVED ISSUES REQUIRING FURTHER DISCUSSION:

There were no unresolved issues requiring further discussion.

#### ACTION ITEMS:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>	<u>Completion Date</u>
1. Send consult to DODP.	OPD	ASAP	<u>✓ 8-25-99</u>
2. Provide a draft of Division's response to OPD memo before sending an official version.	S.Honig	by 8-25-99	<u>✓ 8-25-99 via e-mail</u>
3. Route Division's draft to D.Fox (OCC).	D.Spillman	After item #2 is completed.	<u>✓ 8-25-99 via e-mail</u>

The meeting concluded at approximately 3:30 p.m.

/s/ 10/1/99 Concurrence Chair: /s/ 10/1/99  
Dianne Spillman /date Julie Beitz, M.D. /date  
Project Manager/ Minutes preparer Acting Deputy Director (thru 9-25-99)

cc: Original NDA 50-778  
HFD-150/Div.Files  
/Action package

Draft: D.Spillman/10-1-99  
Thru: J.Beitz/10-1-99  
F/T by: dds/10-1-99  
c:\...\50778\mtgs\990824imm-orphan

**MEETING MINUTES = OTHER (O):**  
**Internal**

**DDR: DO NOT DISTRIBUTE COPIES  
TO THESE PEOPLE**

electronic copy only: /J.Beitz  
✓ done 10/1/99 /G.Williams  
/S.Honig  
/R.Justice  
/D.Pease  
/L.Vaccari  
/R.Temple (ODEI / HFD-101)  
/J.McCormick (OPD / HF-35)  
/M.Lessing (OPD / HF-35)  
/T.Nguyen (OPD / HF-35)  
/H.Startzman (OPD / HF-35)  
/K.Dettelbach (OCC / GCF-1)  
/D.Fox (OCC/GCF-1)

## MEETING MINUTES

**MEETING DATE:** August 16, 1999      **TIME:** 3:00 pm      **LOCATION:** Conf. Rm. G

**NDA 50-778**      Meeting Request Submission Date: July 29, 1999

**DRUG:** ELLENCE (epirubicin hydrochloride)

**SPONSOR/APPLICANT:** Pharmacia & Upjohn

### **TYPE of MEETING:**

Special Considerations – “old” antibiotic classification

### **FDA PARTICIPANTS:**

Dr. Murray Lumpkin – Director, Office of Review Management  
Dr. Robert Temple – Associate Director for Policy  
Ms. Christine Rogers – Regulatory Counsel  
Mr. David Fox – General Attorney  
Dr. Renata Albrecht – Acting Deputy Director, ODE IV  
Dr. Tom Hassell – Asst. Dep. Reg. Health, ODE IV  
Dr. Lillian Gavrilovich – Deputy Director, DAIDP  
Dr. James King – Microbiologist, DAIDP  
Dr. Jim Timper – Chemistry Reviewer, DAIDP  
Dr. Hasmukh Patel – DNDC I  
Dr. John Simmons – Director DNDC I  
Dr. Grant Williams – Medical Team Leader  
Ms. Leslie Vaccari – Assistant to the Director, DODP  
Mr. Patrick Guinn – Project Manager

### **INDUSTRY PARTICIPANTS:**

Larry Moore – Pharmacia and Upjohn  
Ken King – Pharmacia and Upjohn  
Daniel Mannix – Pharmacia & Upjohn

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### **BACKGROUND:**

Pharmacia & Upjohn submitted a New Drug Application (NDA) on December 15, 1998, for epirubicin hydrochloride. Upon receipt of the application, epirubicin was assigned as NDA 21-010 and during the review process, epirubicin was noted to be an antibiotic and was reassigned as NDA 50-778. Once the NDA was reassigned as an antibiotic, it was also determined that epirubicin would be considered an “old” antibiotic according to The Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug and Cosmetic

Act. This guidance document states that an antibiotic application received by the Secretary, on or before November 20, 1997, is considered an "old" antibiotic. An application for epirubicin was originally submitted on July 24, 1984, by Farmatolia and subsequently, received a Not Approvable. Pharmacia & Upjohn chose not to address the NA issues. Additional studies were performed and the new data was submitted as a new application.

Upon learning that the classification of epirubicin as an "old" antibiotic represented a barrier to Waxman/Hatch exclusivity, Pharmacia & Upjohn requested that the Agency reconsider the classification of epirubicin as an "old" antibiotic. The sponsor has submitted several documents that provided additional information for our consideration.

In addition, Pharmacia & Upjohn had filed for orphan drug designation on December 11, 1998, and recently received a letter denying that request. Upon appeal of the decision, Pharmacia & Upjohn was informed that the original decision not to designate epirubicin an orphan drug for the treatment of stage II node-positive and stage III breast cancer would remain unchanged. Pharmacia & Upjohn is still interested in pursuing this issue further.

Currently, NDA 50-778 for ELLENCE (epirubicin hydrochloride) Injection is under review. The application received a priority review status and was originally due June 15, 1999, however, the Agency received a major amendment June 9, 1999, and the User Fee Date was extended to September 15, 1999.

#### **MEETING OBJECTIVES:**

To discuss the policy on antibiotic classification, what constitutes an "old" antibiotic and in particular, how this relates to epirubicin.

#### **DISCUSSION and DECISIONS REACHED:**

Pharmacia & Upjohn believes that they deserve some economic protection rights for the development of epirubicin. At this time, there are two options that could be considered. The first option would be for the Agency to reconsider its judgement that epirubicin is an antibiotic, leading to 5 years exclusivity under Waxman/Hatch. The second option is for the Agency to reconsider its denial of the orphan drug application, leading to 7 years exclusivity.

- There was a lengthy discussion pertaining to the interpretation of the term "antibiotic drug".

According to 201(jj) of the Federal Food, Drug and Cosmetic Act, "The term 'antibiotic drug' means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline,

chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof."

Both Pharmacia & Upjohn and the Agency agreed that the definition of an "antibiotic drug" could be interpreted in various ways. At this time epirubicin is designated as an "antibiotic drug", however, the Agency will consider the points raised during the meeting, by Pharmacia & Upjohn, on how the definition could be interpreted and make a final decision on its classification.

- There was brief discussion pertaining to orphan drug designation.

Pharmacia & Upjohn requested orphan drug designation prior to the submission of NDA 50-778 and subsequently, was denied orphan status. Upon appeal of the decision, Pharmacia & Upjohn received another letter from the Office of Orphan Products Development, dated July 26, 1999, denying orphan status. It was determined that the evidence provided did not substantiate their conclusion that the conditions of Stage II node-positive and Stage III constitute a medically plausible subset of breast cancer for several reasons which were listed in the letter.

Pharmacia & Upjohn believes that they have provided substantial evidence of a medically plausible subset of breast cancer and would like the Agency to reconsider its evaluation and orphan designation status. Agency representatives from the Division of Oncology Drug Products and from the Office of Drug Evaluation I expressed support that they believed that the group of patients receiving adjuvant therapy for breast cancer represented a medically plausible subset of patients. It was agreed that the Division of Oncology Drug Products would discuss this issue with the Office of Orphan Products Development. The Agency has agreed to contact Pharmacia & Upjohn after our internal meeting and will provide information on how Pharmacia & Upjohn will need to proceed.

- It was agreed that if epirubicin receives orphan drug designation, Pharmacia & Upjohn will formally rescind their request, in writing, pertaining to the reconsideration of epirubicin being classified as an "old" antibiotic. In addition, the orphan drug designation must proceed the Action Letter. However, if epirubicin does not receive orphan drug designation, the Agency will need to formally provide the decisions, in writing, pertaining to orphan drug designation and "old" antibiotic classification.
- If Pharmacia & Upjohn receives some exclusivity, the outstanding Chemistry issues will need to be addressed before the Agency can take an Approval Action. However, if the exclusivity issues are not resolved before the User Fee Date of September 15, 1999,

Pharmacia & Upjohn has requested that the Agency issue an Approvable Letter.

**ACTION ITEMS:**

1. The Agency will consider the points raised during the meeting, by Pharmacia & Upjohn, on how the definition of an antibiotic could be interpreted and make a final decision on its classification.
2. An internal meeting between the Division of Oncology Drug Products and the Office of Orphan Products Development will be scheduled. The Agency will contact Pharmacia & Upjohn on how to proceed with this application.
3. The official meeting minutes will be forwarded to Pharmacia & Upjohn from the Agency.

The meeting was concluded at 4:15 pm. There were no unresolved issues or discussion points.

LS  
Patrick Guinn, Project Manager  
Minutes preparer

8/21/99

Concurrence Chair:

LS 9/1/99  
Grant Williams, M.D.  
Medical Team Leader

NDA 50-778  
Meeting Minutes  
Page 5

cc:  
Original NDA 50-778  
HFD-150/Div File  
    /DPease  
    /DSpillman

electronic only cc:

MLumpkin  
RTemple  
CRogers  
DFox  
RALbrecht  
THassell  
LGavrilovich  
JKing  
JTimper  
HPatel  
JSimmons  
RJustice  
JBeitz  
GWilliams  
SHonig  
RWood  
SKim  
LVaccari  
DPease  
DSpillman  
PGuinn

**MEETING MINUTES**

## MEETING MINUTES

MEETING DATE: July 19, 1999      TIME: 9:00 am      LOCATION: Conf. Rm. B

NDA 50-778

Meeting Request Submission Date: June 2, 1999

Briefing Document Date: July 14, 1999

DRUG:            ELLENCE (epirubicin hydrochloride)

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

Internal Meeting; Special Considerations – “old antibiotic” classification

FDA PARTICIPANTS:

Dr. Murray Lumpkin – Director, Office of Review Management  
Ms. Jane Axelrad – Associate Director for Policy  
Ms. Christine Rogers – Regulatory Counsel  
Mr. David Fox – General Attorney  
Dr. Robert Temple – Associate Director of Medical Policy  
Dr. John Simmons – Director, DNDC1  
Dr. Sung Kim – Chemistry Reviewer, DNDC1  
Dr. Lillian Gavrilovich – Deputy Director, DAIDP  
Dr. James King – Microbiologist, DAIDP  
Dr. Jim Timper – Chemistry Reviewer, DAIDP  
Dr. Renata Albrecht – Acting Deputy Director, ODE IV  
Dr. Julie Beitz – Acting Deputy Director, DODP  
Mr. Patrick Guinn – Regulatory Health Project Coordinator, DODP

Background:

Pharmacia & Upjohn submitted a New Drug Application (NDA) on December 15, 1998 for epirubicin hydrochloride. Upon receipt of the application, epirubicin was assigned as NDA 20-010 and during the review process, epirubicin was noted to be an antibiotic and was reassigned as NDA 50-778. Once the NDA was reassigned as an antibiotic, it was also determined that epirubicin would be considered an “old” antibiotic according to The Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act. This guidance document states that an antibiotic application received by the Secretary, on or before November 20, 1997, is considered an “old” antibiotic. An application for epirubicin was originally submitted on July 24, 1984, by Farmatolia and subsequently, received a Not Approvable. Pharmacia & Upjohn, with the concurrence of the Division of Oncology Drug Products, chose

not to address the NA issues, but rather to perform additional studies and submitted the data as a new application.

Pharmacia & Upjohn, then realized, that the classification of epirubicin as an "old" antibiotic represented a barrier to Waxman/Hatch exclusivity. Therefore, Pharmacia & Upjohn requested that we reconsider our classification of epirubicin as an "old" antibiotic. The sponsor has submitted several documents, which are included in this package, that provide additional information for our consideration.

Currently, NDA 50-778 for ELLENCE (epirubicin hydrochloride) Injection is under review. The application received a priority review status and was originally due June 15, 1999, however, the Agency received a major amendment June 9, 1999 and the USER FEE DATE has been extended to September 15, 1999. The Division's goal is to take an Action in August 1999.

**Objective:**

To discuss the policy on antibiotic classification, what constitutes an "old" antibiotic and in particular, how this relates to epirubicin.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**1. Discussion of Pharmacia & Upjohn's June 2, 1999 submission (TAB 2).**

Although Pharmacia & Upjohn performed additional studies and submitted this application on December 15, 1999, as a new NDA (did not submit the application as a response to the Not Approvable), does the Agency still consider receiving epirubicin as an application for a drug that contains an antibiotic, before November 1997?

- Yes. Any dosage form for the moiety is considered as received.

**2. Definition of Antibiotic:**

Any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for use by man containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance) or any derivative thereof.

Does the Agency agree with this definition?

- Yes

**3. Discussion of Pharmacia & Upjohn's July 1, 1999 submission (TAB 5).**

Does the Agency agree that epirubicin meets the first aspect (produced or synthesized from a micro-organism or any derivative thereof) of the definition for antibiotic?

- Yes

**4. Discussion of Pharmacia & Upjohn's June 10 and 11, 1999 submissions (TABs 3 and 4). In addition, Dr. James King's comments on drug classification of epirubicin (TAB 6).**

Does the Agency agree that epirubicin meets the second aspect (has the capacity to inhibit or destroy micro-organisms in dilute solution) of the definition of an antibiotic?

- Yes, epirubicin does have anti-microbial activity.

**5. Discussion of Dr. Marc Cavaille-Coll's review and discussion of antibiotic classifications (TAB 7).**

Does a drug need to meet both aspects of the definition or does meeting only one part constitute the drug as an antibiotic?

- The drug needs to meet both aspects. Epirubicin does meet both.

**6. Discussion of Nipent information (TAB 9).**

If a drug must meet both aspects of the definition in order to be considered an antibiotic, can we assess the classification in a similar way as Nipent?

- Not applicable because epirubicin meets both aspects.

**7. If epirubicin does not meet both criteria can we reclassify epirubicin from an antibiotic to a non-antibiotic?**

- Not applicable because epirubicin meets both criteria.

**8. How should we deal with the other applications similar to epirubicin (e.g., daunorubicin, doxorubicin, etc.) that have already been submitted? That will be submitted in the future?**

- Not applicable because the Agency has determined that there is no need for

reclassification.

Additional Questions:

1. Does this relate to Nipent? Was it classified correctly?
  - Looking at the literature and the in vitro data submitted, Nipent was classified correctly.
2. Will we meet with Pharmacia & Upjohn? At what level?
  - We could provide the sponsor with our tentative decision in a letter and offer to meet with them.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- Contact Orphan Products and obtain an update on orphan designation consideration.


ACTION ITEMS: (Include description, identify person responsible and due date.)

1. Chris Rogers will draft a letter to be sent to the sponsor with our tentative decision.
2. Patrick Guinn will contact Orphan Products for an update.
3. Patrick Guinn will provide the final meeting minutes for this internal meeting.

The meeting was concluded at 10:00 am.

  
Patrick Guinn, Project Manager  
Minutes preparer

Concurrence Chair: \_\_\_\_\_

 8/11/99  
Julie Beitz, M.D.  
Acting Deputy Director, DODP

NDA 50-778  
Meeting minutes  
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cc:  
Original NDA 50-778  
HFD-150/Div File  
    /JBeitz  
    /DPease  
    /PGuinn  
    /DSpillman

cc: electronic only

Dr. Murray Lumpkin – Director, Office of Review Management  
Ms. Jane Axelrad – Associate Director for Policy  
Ms. Christine Rogers – Regulatory Counsel  
Mr. David Fox – General Attorney  
Dr. Robert Temple – Associate Director of Medical Policy  
Dr. John Simmons – Director, DNDC1  
Dr. Rebecca Wood – Chemistry Team Leader, DNDC1  
Dr. Sung Kim – Chemistry Reviewer, DNDC1  
Dr. Gary Chikami – Supervisory Medical Officer, DAIDP  
Dr. Lillian Gavrilovich – Deputy Director, DAIDP  
Dr. Albert Sheldon – Supervisory Microbiologist, DAIDP  
Dr. James King – Microbiologist, DAIDP  
Dr. Jim Timper – Chemistry Reviewer, DAIDP  
Dr. Renata Albrecht – Acting Deputy Director, ODE IV  
Dr. Robert Justice – Acting Director, Division of Oncology Drug Products  
Dr. Julie Beitz – Acting Deputy Director, DODP  
Dr. Grant Williams – Medical Team Leader, DODP  
Dr. Susan Honig – Medical Officer, DODP  
Ms. Dotti Pease – Chief, Project Management Staff, DODP  
Ms. Leslie Vaccari – Assistant to the Director, DODP  
Mr. Patrick Guinn – Regulatory Health Project Coordinator, DODP

MEETING MINUTES

## MEETING MINUTES

MEETING DATE: May 12, 1999    TIME: 11:00 am    LOCATION: Conf. Rm. B

NDA 21-010

DRUG: epirubicin hydrochloride for Injection

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. 5 month Team meeting
2. Proposed Indication: Treatment of locally advanced or metastatic breast cancer

FDA PARTICIPANTS:

Robert Justice, M.D. – Acting Division Director

Grant Williams, M.D. – Medical Team Leader

Susan Honig, M.D. – Medical Officer

Paul Andrews, Ph.D. – Pharmacology Team Leader

Doo Young LeeHam, Ph.D. – Pharmacology Reviewer

Gang Chen, Ph.D. – Biometrics Team Leader

Ruthann Davi, Ph.D. – Biometrics Reviewer

MEETING OBJECTIVES:

1. To discuss DSI issues and action required by the team.
2. To determine when labeling reviews will be completed and when to schedule a labeling meeting.


Meeting Discussion:

1. To discuss DSI issues and action required by the team.
  - Informed Consent and Tumor Measurements: Gus Turner and DSI to decide if the responses to the audit issues are acceptable. Once it has been determined whether the responses are acceptable/not acceptable, the team will discuss with Gus Turner if additional sites should be audited.
  - Grant Williams, Medical Team Leader, sent a request for additional consultation to Gus Turner on May 13, 1999.

NDA 21-010  
5 month Meeting  
page 2

2. To determine when labeling reviews will be completed and when to schedule a labeling meeting.
  - All labeling reviews should be completed and submitted to Patrick Guinn, Project Manager, by May 28, 1999. The labeling comments will be incorporated into one document for review and then forwarded to the sponsor by June 2, 1999.

The meeting was concluded at 11:30 am. There were no unresolved issues or discussion points.

  
\_\_\_\_\_  
Project Manager  
Minutes preparer

MEETING MINUTES

NDA 21-010 epirubicin hydrochloride for injection

4 Month Team Meeting

**CANCELLED**

## MEETING MINUTES

MEETING DATE: March 17, 1999 TIME: 11:00am LOCATION: Conf. Rm. B

NDA 21-010

DRUG: epirubicin hydrochloride for Injection

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. 3 month Team meeting
2. Proposed Indication: Treatment of locally advanced or metastatic breast cancer

FDA PARTICIPANTS:

Robert Justice, M.D. – Acting Division Director  
Grant Williams, M.D. – Medical Team Leader  
Susan Honig, M.D. – Medical Officer  
Paul Andrews, Ph.D. – Pharmacology Team Leader  
Doo Young LeeHam, Ph.D. – Pharmacology Reviewer  
Atik Rahmana, Ph.D. – Biopharmaceutics Team Leader  
Safaa Ibrahim, Ph.D. – Biopharmaceutics Reviewer  
Gang Chen, Ph.D. – Biometrics Team Leader  
Ruthann Davi, Ph.D. – Biometrics Reviewer  
Rebecca Wood, Ph.D. – Chemistry Team Leader  
Sung Kim, Ph.D. – Chemistry Reviewer

MEETING OBJECTIVES:

1. To determine what information is still required from the sponsor.
2. To discuss any issues that need to be addressed as a team.
3. To determine timelines and review completions.
4. To determine when labeling reviews will be completed and when to schedule a labeling meeting.

Meeting Discussion:

1. To determine what information is still required from the sponsor.  
**Medical** - None  
**Biometrics** – Still waiting for electronic data from recent submissions  
**Chemistry** - None

**Biopharmaceutics - None**

**Pharmacology - None**

**Audits – EA,EER,micro all requested**

**Consults – DSI requested**

2. To discuss any issues that need to be addressed as a team.

**Medical - None**

**Biometrics - None**

**Chemistry – The formulation may be very old; Clinical studies may be different from the current formulation**

**Biopharmaceutics - None**

**Pharmacology - None**

3. To determine timelines and review completions.

ODAC Meeting June 7/8, 1999. User Fee Date June 15, 1999.

**Medical – May 15, 1999**

**Biometrics - May 15, 1999**

**Chemistry – End of May**

**Biopharmaceutics – End of May**

**Pharmacology – End of May**

4. To determine when labeling reviews will be completed and when to schedule a labeling meeting.

**Medical – April 15, 1999 changed to May 3, 1999**

**Biometrics – April 15, 1999 changed to May 3, 1999**

**Chemistry – April 15, 1999 changed to May 3, 1999**

**Biopharmaceutics – April 15, 1999 changed to May 3, 1999**

**Pharmacology – April 15, 1999 changed to May 3, 1999**

**Labeling Meeting scheduled for April 21, 1999 changed to May 5, 1999.**

The meeting was concluded at 11:30 am. There were no unresolved issues or discussion points.

/S/

4/29/99

Project Manager

Minutes preparer

MEETING MINUTES

## MEETING MINUTES

MEETING DATE: January 28, 1999 TIME: 1:00pm LOCATION: Conf. Rm. B

NDA 21-010

DRUG: epirubicin hydrochloride for Injection

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. 45 day filing meeting
2. Proposed Indication: A component of adjuvant therapy in patients with evidence of axillary-node-tumor involvement following resection of primary breast cancer (Stage II & III) and for the therapy of patients with locally advanced or metastatic breast cancer.

### FDA PARTICIPANTS:

Robert Justice, M.D. – Acting Division Director  
Grant Williams, M.D. – Medical Team Leader  
Susan Honig, M.D. – Medical Officer  
Paul Andrews, Ph.D. – Pharmacology Team Leader  
Doo Young LeeHam, Ph.D. – Pharmacology Reviewer  
Atik Rahmana, Ph.D. – Biopharmaceutics Team Leader  
Safaa Ibrahim, Ph.D. – Biopharmaceutics Reviewer  
Gang Chen, Ph.D. – Biometrics Team Leader  
Ruthann Davi, Ph.D. – Biometrics Reviewer  
Rebecca Wood, Ph.D. – Chemistry Team Leader  
Sung Kim, Ph.D. – Chemistry Reviewer

### MEETING OBJECTIVES:

1. To determine the fileability of the application.
2. To determine what information is still required from the sponsor.
3. To determine timelines and review completions.

### Meeting Discussion:

1. To determine the fileability of the application.  
**Medical** - Fileable  
**Biometrics** – Fileable  
**Chemistry** - Fileable

**Biopharmaceutics** - Fileable

**Pharmacology** – Fileable

2. To determine what information is still required from the sponsor.

**Medical** – Comments to be conveyed (completed 1-29-99)

**Biometrics** – Provide a copy of volume 2.2 to Gang Chen (completed 1-28-99)

**Chemistry** – Comments to be conveyed (completed 1-29-99)

- Need volume 2.8 for Microbiology consult (completed 1-29-99)

**Biopharmaceutics** - None

**Pharmacology** – Provide Dr. Lee-Ham with the old epirubicin NDA (completed 1-28-99)

**Consults** – DSI should be requested (completed 1-29-99)

**Other** - Provide the team with an electronic version of the label (completed 1-29-99)

3. To determine timelines and review completions.

ODAC Meeting June 7/8, 1999. User Fee Date June 15, 1999.

**Medical** – May 15, 1999

**Biometrics** - May 15, 1999

**Chemistry** – End of May

**Biopharmaceutics** – End of May

**Pharmacology** – End of May

The meeting was concluded at 1:30 pm. There were no unresolved issues or discussion points.




Project Manager

Minutes preparer

MEETING MINUTES

## MEETING MINUTES

MEETING DATE: July 23, 1998      TIME: 12:30 pm      LOCATION: Conf. Rm. B

IND  Meeting Request Submission Date: May 18, 1998  
Briefing Document Submission Date: June 30, 1998

DRUG: Epirubicin Hydrochloride

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. Pre-NDA CMC
2. Proposed Indication: Adjuvant treatment of patients with node-positive early breast cancer and for the treatment of patients with advanced/recurrent breast cancer

### FDA PARTICIPANTS:

Dr. Simmons	- Deputy Director
Dr. Zhou	- Chemistry Team Leader
Dr. Liang	- Chemistry Reviewer
Dr. X.Chen	- Chemistry Reviewer
Dr. Chidambaram	- Chemistry Reviewer
Mr. P.Guinn	- Project Manager

### INDUSTRY PARTICIPANTS:

Carlo Confalonieri -Head of Pharmaceutical Controls, Pharmaceutical Development, Italy  
Attilio Tomasi - Head of Chemical Department, Bulk Process R&D, Italy  
Jerry Walker - Global Supply API Process R&D Leader  
Tom Zwier - Global Supply API Quality Assurance Leader  
Mark VanArendonk -Director, North America Pharmaceutical Development QA  
Alberto Fittipaldo - Project Leader  
Mark Griso- Director, Global Regulatory Affairs  
Denise Tindle - Global Regulatory Affairs Manager

### MEETING OBJECTIVES:

To discuss the plans for a submission of an NDA for epirubicin hydrochloride for the treatment of breast cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. API stability data

In the NDA, Pharmacia and Upjohn will present:

- Long term (10 batches) and accelerated (3 batches) API stability data from commercial scale batches of the current process.
- Data demonstrating the chemical and physical equivalence of API from the current and NDA processes.
- Three months of comparative accelerated stability data for API from the current and NDA processes (commercial scale batches).

Does FDA consider that this package will be sufficient to support filing of an NDA for Pharmorubicin CS?

- ⇒ Yes. The Agency agrees with the package. However, additional updated primary stability test data will need to be submitted during NDA review.
- ⇒ In the stability section, the data should be provided in a tabular form and not as an attachment for easy review. It should include test method, impurity profile, lot numbers (clinical trial vs. commercial product), site and date of manufacture, etc.
- ⇒ Please clarify what you mean by chemical and physical equivalence.

2. API Specifications and Batch Analyses

A rationale will be provided in the NDA to support the proposed API specifications and will include the following elements:

- The batch results of the first five batches of yearly production from 1993 to 1998 ( — ) , plus the results of all batches made according to the NDA process available at the time of submission.
- The stability data discussed above which provides an indication of the identity and amounts of impurities in the API batches used to manufacture the product batches used in the clinical trials.

- Cross references to safety data from toxicology studies.
- Consideration of the assay method variability.

Does the FDA agree that the data to be provided in the rationale will be sufficient to review and approve specifications for the API?

⇒ Yes. The data seem acceptable at this point to support a submission. However, additional test data should be provided and the limits may need to be negotiated at a later time.

⇒ In addition, we request that you:

- \* Justify proposed specifications.
- \* Provide justification of including/not including melting point and optical rotation in specifications.

### 3. Quality of lots used in clinical trials

The pivotal and supporting studies for this New Drug Application were carried out by investigators and institutions during the period 1989 - 1995 in countries where Epirubicin Hydrochloride was legally marketed. Freeze-dried product used for these trials was therefore taken from local pharmacy stock and the batches employed cannot be reconciled to the studies. We believe a review of the data described in the following three points defines the quality of the lots used in the clinical trials and supports the product intended for marketing:

- A quality overview of all production lots of freeze-dried products manufactured in the period 1990-1998 \ — \ and the first five batches manufactured in years 1988 and 1989.
- A similar quality overview for the ready-to-use formulation, covering the period 1991 - 1998 \ — \ in order to compare the quality of the product used in clinical trials vs. the NDA formulation.
- The analytical certificates of the lots of ready-to-use solution used for the tolerability study.

Does FDA agree that the quality of the product used in the clinical trials is characterized sufficiently by these data to support filing of an NDA for Pharmorubicin CS?

⇒ Yes. It appears that it could support filing. However, a more detailed discussion of quality and quantity of data will be needed.

⇒ In this discussion:

- \* Please clarify whether the data is from the same site/scale/formulation.
- \* Clarify what you mean by clinical trials vs. the NDA formulation.

#### 4. Finished product stability data

The stability package in the NDA will include:

- 3 months refrigerated stability data and up to 6 months at 25°C on 6 pilot scale lots packed in plastic vials manufactured starting from current process API.
- 3 months refrigerated stability data on 3 commercial batches packed in glass vials manufactured starting from current process API.
- 3 month refrigerated and 25°C stability data on 3 pilot scale lots packed in plastic vials manufactured starting from NDA process API; plus similar stability data on 3 pilot batches packed in glass vials. (A complete review of the 6 month accelerated data will be provided in March 1999)

Does FDA agree that the data to be provided in the NDA will be sufficient for review and approval of a tentative expiration dating period?

⇒ It is adequate for review. However, before a decision can be made regarding the approvability of a tentative expiration dating period, the information must be submitted and reviewed.

⇒ In general, the FDA requires data from the production scale lots.

⇒ In addition, please provide:

- \* Information about manufacturing scale (pilot scale, industrial batch, commercial scale, etc.) in your submission.
- \* How many lots (for each strength) you intend to use for your stability study.

- \* The proposed stability protocol for the drug substance and drug product.
- \* A commitment to provide stability data on the first three commercial lots from each strength of the drug product.

#### 5. Environmental assessment

The amount of Epirubicin Hydrochloride expected to be released into the aquatic environment at maturity — is less than 1 ppb. P&U therefore proposes to claim for categorical exclusion submitting only these calculations of estimated concentration at the point of entry into the aquatic environment.

Is this deemed acceptable by FDA for environmental assessment evaluation?

⇒ It is acceptable at this point. However, you still need to submit a claim for categorical exclusion in your NDA.

#### FDA Additional Comments:

1. — should provide appropriate release specifications.  
  
Does — intend to file a Type 2 DMF in the future.  
  
⇒ No.
2. Please provide detailed information on Daunorubicin Hydrochloride — or cross reference it to a DMF. Specification should also include optical rotation and melting point information.
3. Propose plausible mechanisms for the formation of various impurities.
4. Limits on — in drug substance should be proposed/justified.
5. List individual impurities in the specifications for drug substance and drug product.
6. Please clarify the differences in pH between PFS and lyophilized product (after reconstitution).

⇒ Provided in the meeting package.